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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/167,088	10/06/98	FINKELMAN F	91830/625

HM12/0707

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EXAMINER	
GABEL, G	
ART UNIT	**PAPER NUMBER**
1641	3

DATE MAILED: 07/07/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/167,008	Applicant(s) Finkleman et al.
	Examiner Gailene R. Gabel	Group Art Unit 1641

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-42* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-42* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because the application serial number and the filing date are missing.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step a has improper antecedent basis problem in reciting "injecting a human". Change to --injecting the human-- for proper antecedent basis. Furthermore, claim 1, step a is indefinite by reciting "an appropriate amount of targeting moiety" because there is no comparative basis for defining the metes and bounds of the term "appropriate".

Claim 1, step b is indefinite in reciting "time sufficient to bind the target analyte of interest" because it does not provide a comparative basis to define the metes and bounds of the term "sufficient".

Claim 1, step c, is indeterminate in reciting "without dissociation of the target analyte from the targeting moiety" because in the previous step, the targeting moiety and the target analyte have supposedly conjugated so that it is unclear as to what the applicants intend to imply.

Claim 1, step e lacks antecedent basis in reciting "the assay mixture". Claim 1, step e recites the limitation "immobilized capture moiety". There is insufficient antecedent basis for this limitation in the claim since there is no previous indication that the capture moiety is immobilized. Furthermore, claim 1, step e is indefinite in reciting "the immobilized capture moiety to bind specifically to either the target analyte ***or*** the labeled targeting moiety" since the step b indicates a complex formation in vivo between the target analyte and the targeting moiety. Same analogous comment applies to claim 1, step f.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The detection of the target analyte using detection labels in order to determine the amount of target analyte in the sample.

Claim 8 recites overlapping Markush language. Furthermore, claim 8 is indeterminate in scope by reciting "paratopic molecules, recombinant molecules with binding sites".

Claims 20, and 22-24 are indefinite and inconsistent as to the correlative relationship between "another molecule" in claim 20, "the molecule capable of binding... is an antibody" in claim 22, and "the polyclonal antibody" in claim 23, and "the capture moiety is an antibody" in claim 24. The claims do not consistently state the correlative relationship, if there is, between all aforementioned entities.

Claim 25 recites the limitation "detecting the bound conjugate on the *solid support*". There is insufficient antecedent basis for this limitation in the claim.

Claim 34 is indefinite in reciting "A reagent kit useful in performing the method of claim 1". The term "useful" is a relative term which has no comparative basis for defining its metes and bounds. See also claim 37.

Claim 34 is indeterminate in scope by reciting "targeting moiety specific for the *target analyte*" and "contains the standard for the *analyte*" since the claim does not specifically identify the metes and bounds of the "target analyte".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al. (US 5,587,294) in view of Finkelman et al. (Journal of Immunology 151: 1235-1244 (1993), and in further view of Pouletty et al. (US 5,612,034).

Tamarkin et al. disclose a competitive solid phase immunoassay for measuring the concentration of proteins, especially endogenous cytokines in the blood and other body fluids such as saliva, nasal secretions, tears and sweat if humans and animals (see Summary). The immunoassay may be enzyme immunoassay or it may utilize other labels such as fluorescent labels, radioactive elements, or luminescent labels (see column 7, lines 13-20, column 11, line 13 to column 12, line 11). Thereafter, the detection of the labeled antibody or binding partner for the labeled analyte is accomplished by a chromogenic substrate, fluorometer, or a scintillation counter (see column 12 20-29). Tamarkin et al disclose that in polyclonal-antibody based "one-site" immunoassay wherein a cytokine may be bound to another molecule (such as cytokine binding proteins) in the biological fluid, there is at least one part of the molecule that is available

for site recognition (see column 9, lines 10-16). Initially, the body fluid sample is incubated in the presence of an antibody capable of binding to the cytokine and then the amount of cytokine-bound or unbound antibodies are measured (see column 9, lines 48-53). A polyclonal antibody which recognizes many epitopes on the cytokine molecule is adsorbed to a solid phase support or carrier. This polyclonal antibody is the capture antibody which is used to bind the labeled analyte, i.e. biotinylated IL-1, in order to form an antibody-analyte complex (column 10, lines 18-43). The amount of cytokine in the complex is detected by the addition of streptavidin conjugated to an enzyme, i.e. alkaline phosphatase, followed by the addition of a chromogenic substrate -nitrophenyl phosphate (see column 10, lines 47-63 and column 11, lines 13-28). Tamarkin et al. further disclose a kit for measuring cytokine incorporating, therewith, biotin as a label, polyclonal capture antibody as the first binding partner, enzyme conjugated streptavidin as the second binding partner (see column 14, lines 38-46). Tamarkin et al. further discloses the use of a kit incorporating therein all necessary reagent for use in measuring cytokine production in body fluids. Tamarkin et al. fails to teach injecting targeting moiety to a human or animal in order to form a targeting moiety: target analyte complex.

Finkelman et al. teach injecting cytokine- anti-cytokine antibody complexes into the blood stream (see Summary). Finkelman et al. specifically teaches that anti-cytokine antibodies that block interactions between cytokines and cytokine receptors have been used to inhibit endogenous cytokine function. Furthermore, injection of IL-4 and either of two neutralizing anti-IL-4 monoclonal antibody at a cytokine- anti-cytokine monoclonal antibody molar ratio of 2:1

prolongs in vivo IL-4 activity. Complexes that contain as little as 400 NG of IL-4 have considerable in vivo stimulatory activity. Finkelman et al. teach that these observations suggest that complexes of cytokines and neutralizing anti-cytokine monoclonal antibody increase the magnitude and duration effects in vivo. Figure 2 illustrates how complexes of IL-4 and a neutralizing anti-Il-4 monoclonal antibody stimulate greater increase in splenocyte Ia expression than free IL-4 wherein spleen cells from individual mice were stained with FITC-labeled anti-Ia monoclonal antibody and analyzed for fluorescence intensity with a FACScan.

Pouletty et al. (US 5,612,034) disclose injecting binding entities and active agents into the bloodstream of mammalian hosts for covalent bonding to proteins and blood components. Initially, a bolus of a first compound comprising a chemically reactive group and a first binding entity will react with active functionalities of blood components, thereby, creating a population of vascular functionalized blood components. During the lifetime of the functionalized blood components, a second compound may be added which will bind to the first binding entity.

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teachings of Finkleman et al. in the stimulatory effects of injecting cytokine-anti-cytokine antibody complexes into the teachings of Pouletty et al. in administering binding entities with active agents for the purpose of functionalizing proteins, and incorporate both teachings into the method of Tamarkin et al. using competitive solid phase immunoassay for measuring concentration of endogenous cytokines in order to obtain an accurate measure of in vivo production of cytokines in body fluids. One of ordinary skill in the art would have been

motivated to combine the teachings of both Finkleman and Pouletty for the purpose of enhancing in vivo production as well as extending in vivo life span of cytokines, and incorporate therewith the method of Tamarkin et al. utilizing polyclonal-antibody based "one-site" immunoassay in measuring cytokine concentration in order to achieve non-invasive, in vitro, yet accurate assessment of in vivo cytokine production. Furthermore, It would have been obvious to one of ordinary skill in the art to modify the method and kit arrangement of Tamarkin et al, to reflect the teachings of both Finkleman and Pouletty because test kits are conventional and well known in the art for their recognized advantages of convenience and economy.

Remarks

Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

Ruedl et al. teach a detection of secreted cell products using time-resolved fluorescence.

Mukaida et al. teach a solid phase enzyme-linked immunosorbent assay for interleukin-1a using a combination of polyclonal antibody as the immobilized antibody, biotinylated monoclonal antibody as the second antibody and avidin-peroxidase.

Morris et al. teach effects of interleukin-12 in vivo cytokine gene expression and immunoglobulin isotype selection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

GRGabel 7-6-99

Gailene R. Gabel
Patent Examiner
Art Unit 1641

Christopher L. Chin

CHRISTOPHER L. CHIN
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